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Inhaled budesonide in pulmonary sarcoidosis: a double-blind, placebo-controlled study

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Inhaled budesonide in pulmonary sarcoidosis: a double-blind, placebo-controlled study. C. Alberts, Th.W. van der Mark, H.M. Jansen and the Dutch Study Group on Pulmonary Sarcoidosis. ©ERS Journals Ltd 1995.

ABSTRACT: In a double-blind, placebo-controlled study, we assessed the efficacy of inhaled budesonide on the course of newly diagnosed pulmonary sarcoidosis and whether budesonide treatment could postpone oral corticosteroid treatment. We evaluated: 1) symptoms; 2) chest radiography; 3) angiotensin-converting enzyme (ACE) in serum; and 4) lung function.

Patients with histologically confirmed pulmonary sarcoidosis with chest radiographic stages I, II or III, and with an abnormal lung function (inspiratory vital capacity (IVC) <79% of predicted or transfer factor of the lungs for carbon monoxide ($T_{L,CO}$) <77% pred) were included. Patients with radiographic stage II or III but with normal lung function were included when more than 20% of the total cell population in bronchoalveolar lavage fluid (BALF) was lymphocytes.

Forty seven patients received placebo or budesonide (1.2 mg) once daily *via* a Nebuhaler for 6 months, followed by 6 months without treatment. Based on predetermined criteria, 11 patients were excluded during the blind treatment period as they needed oral prednisone: seven (28%) patients in the placebo group (n=25) and four (18%) patients in the budesonide group (n=22). Patient's Global Clinical Impression (GCI) score showed a significant difference in favour of budesonide. IVC showed a significant difference of 7.9% predicted between the two groups during the active treatment period. This difference persisted during follow-up, when the difference was 9.4% pred. $T_{L,CO}$ remained nearly unchanged over time, with no difference between the groups. Improvements in chest radiographic appearance and changes in serum ACE were similar for the two groups.

We conclude that, in patients with pulmonary sarcoidosis, inhaled budesonide results in better subjective symptom scores and a significant improvement of IVC. These findings are in support of a role for inhalation of corticosteroids in pulmonary sarcoidosis, as they may reduce deterioration and postpone the need for systemic corticosteroids.

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The natural course of pulmonary sarcoidosis is variable and frequently spontaneous recovery occurs. Systemic corticosteroid treatment is commonly used in patients with pulmonary sarcoidosis with radiographically determined stages II and III and with respiratory symptoms, or with impaired or deteriorating lung function during an initial observation period without therapy [1, 2]. The aim of such therapy is to alleviate symptoms and to prevent irreversible pulmonary fibrosis by suppressing the granulomatous inflammation. However, long-term treatment with systemic corticosteroids has to be avoided because of possible serious side-effects.

Previous clinical open pilot studies [3–6] have indicated that inhaled corticosteroids, such as budesonide, may have a favourable influence on the course of pulmonary sarcoidosis, with minimal side-effects. However, due to the interpatient variation and the spontaneous fluctuation in disease state, a double-blind comparative study is needed to document the efficacy.

To the best of our knowledge, three small placebo-controlled studies [7–9] on the effect of inhaled budesonide in pulmonary sarcoidosis have been reported. These studies have, in particular, documented that such therapy is effective in modulating the sarcoid-related cellular aberrations in the lung, and provides clinical benefit despite the lack of significant physiological changes.

It may be of value to start early with inhaled corticosteroids in patients with an active form of pulmonary sarcoidosis in order to increase the (spontaneous) improvement rate. The aim of the present double-blind, placebo-controlled study was to assess the effects of inhaled budesonide in patients with newly diagnosed pulmonary

sarcoidosis, and to evaluate whether inhaled budesonide therapy could avoid or diminish the need for treatment with oral corticosteroids.

Materials and Methods

The study, which was of double-blind, placebo-controlled design, was carried out in 14 hospitals in the Netherlands. The inclusion criteria for the study were: a) out-patients of either sex, aged 20–65 yrs; b) newly diagnosed pulmonary sarcoidosis (within 6 months before entering the study), biopsy-proven by histology as established by the local pathologist, and confirmed by an independent pathologist; c) chest radiographic stages I, II or III; and d) abnormal lung function, either a decrease in inspiratory vital capacity (IVC) below 79% of predicted or in transfer factor of the lungs for carbon monoxide ($T_{L,CO}$) below 77% pred. Patients fulfilling the first two criteria, but without lung function impairment, were still included when they had chest radiographic stage II or III, and showed more than 20% lymphocytes in the recovered bronchoalveolar lavage fluid (BALF). Exclusion criteria were: 1) severe symptoms requiring immediate systemic corticosteroid treatment; 2) extrapulmonary manifestations of the disease requiring treatment; 3) obstructive airway disease (forced expiratory volume in one second (FEV_1)/IVC below 85% pred); 4) pregnancy; 5) other concomitant disease, and 6) treatment with oral corticosteroids in the preceding 3 months.

Patients fulfilling the criteria were randomly allocated to either the placebo group or the active treatment group. They received inhaled placebo or budesonide (1.2 mg, six puffs of 0.2 mg) once daily *via* a Nebuhaler for 6 months, followed by 6 months without treatment. The once daily inhalation of this dosage was chosen to achieve an initially high tissue concentration [10].

The criteria for switching to treatment with oral corticosteroids (prednisone) were the occurrence of severe symptoms accompanied by either deterioration of chest radiograph appearance or deterioration in lung function (either a decrease in IVC of ≥8% pred below the initial IVC, or a decrease in $T_{L,CO}$ of ≥10% pred below the initial $T_{L,CO}$). At any time during the 12 months of the study, the chest physician could decide to start treatment with prednisone when the criteria were fulfilled.

Patients attended the out-patient clinic at three monthly intervals for chest radiography, laboratory investigations and lung function measurements. In addition, at each visit to the out-patient clinic the presence or absence of symptoms (malaise, fatigue, arthralgia, dyspnoea and cough) were recorded, from which the total number of symptoms per patient was calculated.

Patients were instructed to keep a case record of any side-effects. The clinical impression regarding the change in severity of symptoms as compared to the previous visit, 3 months previously, was scored by the patient and the chest physician on a 5-point Global Clinical Impression (GCI) scale (much worse; slightly worse; no change; slightly better; much better).

The chest radiographs, performed throughout the study period, were staged according to the conventional descriptive three stage classification of pulmonary sarcoidosis [11]. In addition, after completion of the study, the chest radiographs for each patient were blindly reviewed by the study co-ordinator (C.A.). Also, the descriptive staging method was used, and the severity of radiographic abnormality was subjectively determined, using a rating scale from zero to three (no abnormalities; slight abnormalities; moderate abnormalities; very marked abnormalities). The chest radiographs from individual patients over time were further subjectively classified as deteriorating, stable or improving on a 7-point scale (marked deterioration; moderate deterioration; slight deterioration; no change; slight improvement; moderate improvement; marked improvement). Angiotensin-converting enzyme (ACE) concentrations in serum, obtained at each visit to the out-patient clinic, were determined according to local laboratory techniques. For each patient the percentage of change from the baseline ACE value was calculated.

Lung function measurements included spirometry and transfer factor. The IVC and the FEV_1 were measured with a standard water-sealed spirometer (in 12 centres), or by pneumotachography (in 2 centres). The $T_{L,CO}$ was determined by the single-breath technique of KROGH [12], as modified by OGILVIE *et al*. [13] and COTES [14].

$T_{L,CO}$ values were corrected for haemoglobin concentrations according to COTES [14], in order to obtain $T_{L,CO}$ values under standard conditions. The predicted normal values for spirometry and transfer factor were taken from QUANJER [15]. For non-Caucasian patients a reduction of 10% of the predicted values for Caucasians was applied, based upon the advice of the working party for standardization of lung function tests [15]. The lung function results were expressed in percentages of predicted values to compensate for interpatient differences in race, gender, age and height.

Bronchoalveolar lavage (BAL) was an optional procedure. It was performed in a standard fashion as described by the European Society of Pneumology Task Group on BAL [16]. The values of total and differential cell counts in BALF were determined by standard methods, as described previously [17].

The study was approved by the Medical Ethics Committees of all participating hospitals. Informed consent was obtained from all patients.

Statistical analysis

For the primary end-point of the study, Kaplan-Meier curves were constructed [18]. Patients who withdrew from the study were considered as "lost for follow-up" for the Kaplan-Meier analysis. Parametric variables were analysed with analysis of variance (ANOVA) in a repeated measurement design with time and treatment as factors, and with the centre number as confounding factor. The interaction "treatment * time" was included as a separate factor, since a carry-over effect was expected in the 6 months follow-up period without treatment. Since oral corticosteroid treatment is supposed to have clinical benefit and the blind treatment was not continued after the switch to prednisone, data obtained after the switch to prednisone were considered as "missing" for

ANOVA. The ANOVA was followed by Multiple Classification Analysis, as outlined in SPSS/PC+ [19]. Categorical variables were analysed using χ^2-analysis or Fisher's exact test when appropriate. Values of p less than 0.05 were interpreted as significant.

Power analysis prior to the study was performed on the number of patients with (spontaneous) improvement, estimated to be 30%. During inhaled budesonide therapy an improvement rate of 60% was considered as a clinically relevant effect. With significance α=0.05 and power 1-β=0.80, 50 patients were required in each treatment group. No power analysis was performed on the proportion of patients requiring treatment with oral corticosteroids or on the lung function and BALF parameters.

Results

During a period of 42 months, a total of 47 patients was included in the study. The patients received no treatment in the period between diagnosis and entry. Twenty five patients were allocated to placebo treatment and 22 patients to budesonide treatment. The initial clinical characteristics of the two study groups are presented in table 1. At the time of inclusion, there were no significant differences between the two groups. Six patients with chest radiographic stage II or III, but normal lung function parameters, were enrolled in the study because of an increased percentage (>20%) of lymphocytes in BALF (range 23–77%, median 53%).

A total of nine patients withdrew from the study: three patients during placebo treatment (two withdrawals of consent, one of which followed the switch to prednisone; and one patient lost for follow-up for unknown reasons); four patients during budesonide treatment (three withdrawals of consent, one of which became asymptomatic, one patient after the switch to prednisone, and one patient on the advice of another chest physician; and one patient after an intercurrent disease); two patients were lost for follow-up during the second 6 months period (both patients previously treated with budesonide, and one of which followed the switch to prednisone). Thus, in the group of patients who had to be switched to prednisone, three patients withdrew. From the remaining six withdrawals (not receiving oral corticosteroids), five patients withdrew within 3 months after entry into the study.

Table 1. – Baseline data of all patients receiving either placebo or budesonide inhalation therapy.

		Placebo	Budesonide
Patients n		25	22
Sex M/F		14/11	7/15
Age yrs*		34 (11)	36 (10)
Non-Caucasians n		6	7
Symptoms† per patient* n		3.1 (1.2)	2.5 (1.9)
Chest radiograph stage	I	6	7
	II	14	12
	III	5	3
IVC % pred*		86.6 (16.1)	88.7 (15.8)
$T_{L,CO}$ % pred*		74.3 (14.8)	76.7 (16.6)

*: values are mean (SD). †: symptoms were malaise, fatigue, arthralgia, dypnoea and cough. M: male; F: female; IVC: inspiratory vital capacity; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; % pred: percentage of predicted value.

Oral corticosteroid therapy

During the study, 11 (23%) of the 47 patients had to be switched to oral prednisone treatment: seven (28%) patients in the placebo group and four (18%) patients in the budesonide group. Kaplan-Meier analysis showed that the difference was not statistically significant (p=0.43) (fig. 1). In the budesonide group, the switch to oral prednisone treatment was earlier than in the placebo group (median 77 days *versus* 106 days). There were no switches in treatment regimens during the 6 month follow-up period. In the group where a switch of treatment regimen appeared to be necessary, eight patients had radiographic stage II pulmonary sarcoidosis at entry into the study, and three patients started with stage III. There was no statistically significant difference in the chest radiographic stages in the 11 patients undergoing a switch of treatment regimen, compared to the other 36 patients at entry into the study. In the 11 patients undergoing a switch of treatment regimen, five patients were switched because of deterioration of lung function parameters. All five patients were in the placebo group and no patient in the budesonide group. This difference was statistically significant (p=0.045, Fisher's exact test). In the other six patients the switch was mainly because of chest radiographic deterioration.

Symptoms

Throughout the 6 months of treatment, patients and chest physicians generally reported an improvement in severity of symptoms, which stabilized during the 6 month of follow-up without treatment. Excluding the patients undergoing a switch of treatment regimen, the number

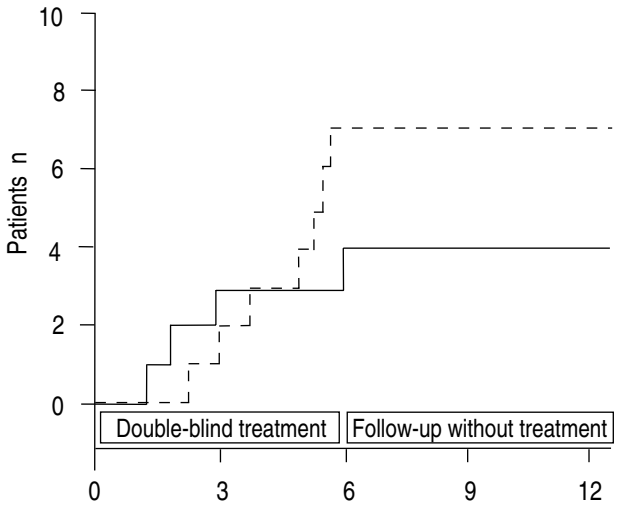

Fig. 1. – Kaplan-Meier analysis. Curves represent the cumulative number of patients switched to oral prednisone therapy in the placebo group (- - -) and in the budesonide group (———) *versus* time.

of individuals who stated after the 6 month treatment period that they felt to be "much better" was seven (47%) in the budesonide group and one (6%) in the placebo group.

The change in severity of symptoms scored on the 5-point GCI scale showed a significant difference in favour of budesonide treatment (p=0.03, χ^2-test). The same GCI score as assessed by the treating chest physicians yielded a tendency towards budesonide treatment (p=0.13). On the latter GCI scale, five (36%) patients in the budesonide group *versus* one (6%) patient in the placebo group were "much better" after the 6 months of blind treatment.

The total number of symptoms (malaise, fatigue, arthralgia, dyspnoea and cough) per patient decreased more rapidly during inhaled budesonide than during placebo treatment, though not all symptoms decreased in a similar way. Persistence of fatigue or cough was reported in some patients for each group. The number of placebo and budesonide treated patients totally free of symptoms at the end of the treatment period was seven (44%) and nine (69%), respectively. The difference between the two groups was not statistically significant (p=0.46, χ^2-test).

Chest radiography

In the two treatment groups, there were slight to marked improvements in chest radiographic appearance. At the end of the 6 months treatment period, the percentage of patients with a "marked" chest radiographic improvement (a chest radiographic stage lower than those at entry into the study) in the budesonide group were 62 and 47% (scored by the independent observer and the treating chest physician, respectively), and in the placebo group 67 and 67% (scored by the independent observer and the treating chest physician, respectively). No further radiographic improvement was observed during the follow-up period for the two groups.

Throughout the 12 months study, there were no statistically significant differences between the two groups with regard to the severity of radiographic abnormalities, nor within time for each group.

Fourteen patients (eight patients on placebo treatment and six patients on budesonide treatment) showed a complete radiographic clearance after 6 months of treatment. In this group of patients, eight patients had radiographic stage I, three patients stage II and three patients stage III pulmonary sarcoidosis at entry into the study. For the majority of stage I patients the chest radiograph became completely clear, whilst a minority of those with stage II and stage III disease cleared during the study.

Laboratory investigations

Levels of serum ACE were reduced during treatment with either inhaled placebo or inhaled budesonide. In the budesonide group, levels of serum ACE increased slightly during the 6 month follow-up period without treatment. Comparison by ANOVA revealed no statistical significance for difference between the two groups (p=0.32), and for the change over time (p=0.94).

Bronchoalveolar lavage was performed in 24 (51%) of the 47 patients at the time of inclusion; 13 patients were randomized to the placebo group and 11 patients to the budesonide group. The median percentages of lymphocytes in BALF were not different between the two treatment groups: 30% (range 2–77%) in the placebo group, and 45% (range 3–60%) in the budesonide group. Four of these 24 patients had to be switched to oral prednisone treatment: all were from the placebo group and showed a median lymphocyte count of only 17% (range 10–25%).

Lung function

Analysis of the effect of budesonide on lung function parameters was limited to patients not withdrawn within 3 months of the study, and not on oral corticosteroids (n=31). Lung function values are given in table 2. Thirty one percent of the patients in the placebo group showed an increase of more than 8% pred from the baseline value, compared to 69% pred in the budesonide group (p=0.01, χ^2-test). The level of 8% pred to define a relevant improvement was chosen in accordance with the prestudy determined criteria for lung function deterioration. The amelioration of IVC appears to be evenly distributed over patients with a restricted IVC and patients with normal IVC. We found a significant difference in IVC between the two treatment groups during the active treatment period. Baseline IVC had no significant influence upon this difference (p=0.34). Analysis of the carry-over effect revealed that, during the follow-up period, the difference between the two treatment groups remained stable (table 2). The contribution of the factor time was not significant (p=0.94). The improvement of IVC showed

Table 2. – Lung function values* of the evaluable patients

	Placebo n=16	Budesonide n=15	p-value†
IVC % pred			
Baseline	87.6 (11.4)	90.5 (16.1)	0.53
Active treatment	91.4 (11.5)	99.3 (16.8)	0.013
Follow-up	91.1 (13.0)	100.5 (15.1)	0.005
$T_{L,CO}$ % pred			
Baseline	74.4 (14.1)	77.9 (17.4)	0.52
Active treatment	80.5 (17.6)	83.3 (13.4)	0.40
Follow-up	80.8 (16.6)	82.7 (17.1)	0.58
FEV_1 % pred			
Baseline	84.3 (11.7)	88.4 (14.9)	0.37
Active treatment	93.2 (11.5)	93.2 (13.6)	0.99
Follow-up	91.1 (14.3)	93.2 (15.5)	0.71

Data are presented as mean (SD). *: values listed for the active treatment and follow-up period have been corrected for the other factors in the ANOVA analysis. Baseline-values were assessed at entry in the study. †: p-values refer to the difference between the two groups in the same period. FEV_1: forced expiratory volume in one second. For further abbreviations see legend to table 1.

no correlation with the different radiological stages, nor with the equally distributed improved chest radiography.

However, ANOVA on $T_{L,CO}$ showed no significant effect of inhaled budesonide. In the two groups, a slight increase in $T_{L,CO}$ during the 6 month treatment period was observed compared to baseline, and the $T_{L,CO}$ remained nearly unchanged thereafter. No change of $T_{L,CO}$ over time was found (p=0.98).

FEV_1 values were not significantly different between the two groups, nor in the active treatment period, or during follow-up (table 2). However, a significant increase in FEV_1 with time was observed (p=0.025).

No drug-related adverse effects were reported during the inhaled therapy regimen. Only one patient discontinued the study due to flu-like symptoms after a few weeks of treatment with inhaled budesonide, which the treating physician considered to be an intercurrent disease. Treatment with oral prednisone induced adverse effects in three patients from the group of patients where a switch of treatment regimen appeared to be necessary; one of these patients had to be hospitalized. However, this may be an underestimate, since three patients immediately withdrew from further follow-up after the switch to prednisone.

Discussion

The present double-blind, placebo-controlled study shows a statistically significant favourable effect of inhaled budesonide on the severity of symptoms (GCI, as scored by the patients), and on the IVC in newly diagnosed patients with pulmonary sarcoidosis as compared to treatment with inhaled placebo. No statistically significant effects of budesonide were found, however, with respect to the chest radiographic appearance, the level of serum ACE and pulmonary transfer factor. Chest radiographic improvement and the reduction of serum ACE occurred equally in the two groups.

The aim of the present study was to assess the efficacy of inhaled budesonide on the course of newly diagnosed pulmonary sarcoidosis. When the study was started, there was only little experience with inhaled corticosteroids in the treatment of pulmonary sarcoidosis [3–5]. In the course of this study, a limited number of additional studies have been published [6–9]. With respect to cellular aspects in BALF, the work of SPITERI and co-workers [8, 9, 20] demonstrated a change in the phenotype and functional characteristics of the alveolar macrophage population, which occurs with the observed decrease in BALF lymphocytosis as well as normalization of the increased T-cell CD4/CD8 ratio noted earlier [3, 7]. The immunocytological changes in BALF were, however, not always associated with any striking improvement in chest radiographic appearance or lung function.

The group of patients under study was a minority of patients with newly diagnosed pulmonary sarcoidosis. On the basis of the inclusion criteria - both radiographic abnormalities and lung function impairment, or chest radiographic stage II or III and an increased percentage of lymphocytes in BALF - we defined a group of patients who had to be considered as potential candidates for therapy with systemic corticosteroids. The assumptions in the study were, thus, that without therapy 30% of the patients in the placebo group would show a spontaneous improvement, and that 35% of the patients would require a switch to the oral prednisone treatment regimen within 6 months. The effect of inhaled budesonide was defined as clinically relevant if an increase from 30 to 60% improvement could be obtained. From these assumptions it was calculated that 100 patients had to be enrolled in the study. However, the present study was discontinued prior to reaching the anticipated number of patients, due to the long time needed to enrol the subjects. A further continuation of the study was considered improper; participating patients needed to know the treatment regimens, and continuation would face changing laboratory techniques, decreasing motivation of the investigators and changing ideas about the treatment of pulmonary sarcoidosis.

The assumption on the percentage of placebo-treated patients requiring oral prednisone treatment was almost correct: 28% instead of 35%. Although not significant, the switch to oral corticosteroid treatment was earlier in the budesonide group than in the placebo group. Moreover, the patients in the budesonide group switched to oral prednisone therapy because of deterioration of their chest radiograph and/or increasing symptoms, without a marked decrease in lung function. It could be conjectured that the deterioration due to the disease in these patients was more rapid, and could not be influenced by inhaled corticosteroids, perhaps with exception of lung function. However, no prognostic signs for a rapid course of the disease could be extracted from the available data.

The proportion of subjectively improved patients, as established by the patient's GCI-score, showed a significant difference between the two treatment groups. Although we selected patients having no extrapulmonary manifestations of the disease, extrathoracic symptoms, such as malaise, fatigue and arthralgia, were included in this parameter. Since these symptoms are related to the underlying disease, it is our opinion that such symptoms should be taken into account in evaluating the course of the disease. In addition, local treatment with a high dose of inhaled budesonide, once daily, results in an initial high tissue concentration [10], which may influence systemic symptoms also.

A clear improvement in IVC (table 2) was found in the budesonide group. This improvement persisted during the 6 month follow-up with no treatment. There existed no increase of IVC over time, since the high p-value found in the analysis for the factor time practically rules out a type II error. It could be possible that the onset of the improvement had already occurred within the first 3 months of active treatment, for which no spirometric data are available. The increase in IVC may be due to a reduction of possible bronchial inflammation due to sarcoidosis. However, since assessment of IVC is performed by a slow inspiratory manoeuvre, it is

unlikely that reduction of bronchial involvement would be reflected by improvement of IVC. Therefore, we ascribe the increase of IVC to a beneficial effect of budesonide on the elastic recoil of lung tissue.

FEV1 showed a modest, though significant, increase over time in the two groups. This might indeed be due to a reduction of bronchial involvement, but the observed increase is of no clinical relevance.

No effect of budesonide was shown on gas transport ($T_{L,CO}$) measurements. An explanation for the observation that the $T_{L,CO}$ does not change during treatment with inhaled budesonide may be that changes in transfer factor occur more gradually. When a single event causes a decrease in $T_{L,CO}$, well-known in the case of interstitial pneumonitis inflicted by bleomycin in patients treated for testicular carcinoma, $T_{L,CO}$ slowly returns to normal values over a period of 2 yrs [21]. This may indicate that the follow-up duration in the present study was not long enough to detect changes in $T_{L,CO}$, in particular, when changes in transfer factor are the consequence of small repetitive damage to the pulmonary parenchyma and followed by repair. A persistent decrease of pulmonary transfer factor has also been observed in patients with Raynaud's phenomenon, with and without an underlying connective tissue disease [22].

It can be argued that the dose of inhaled budesonide was not high enough in the present study. At the onset of the study, however, there existed a fear of systemic side-effects when high doses of inhaled budesonide were applied. As established in healthy and asthmatic subjects, systemic side-effects become apparent at inhaled budesonide doses of 1.6 mg·day^{-1} or more; the inhaled dose of 1.6 mg budesonide·day^{-1} is in fact equivalent to the oral dose of 5 mg prednisone·day^{-1} in terms of ability to suppress plasma cortisol level [23]. The study of Van den Bosch *et al*. [10] has shown that single doses of 1.6 mg budesonide, inhaled *via* a Nebuhaler, result in lung tissue concentrations of budesonide high enough to induce a pharmacological effect, and consequently, a high probability of anti-inflammatory effects. With the current knowledge about the systemic effects of inhaled budesonide, a higher dose than 1.2 mg budesonide·day^{-1} seems acceptable.

In conclusion, a significant positive effect on symptoms as well as on IVC was observed, along with some trends which argue in favour of a positive effect of inhaled budesonide in patients with newly diagnosed pulmonary sarcoidosis. The findings in the present study suggest that the application of local corticosteroids may be effective in reducing deterioration and may, therefore, avoid or diminish the need for therapy with oral corticosteroids. However, further studies are needed to determine the appropriate dose of budesonide, either as single therapy or as a combination with low doses of oral corticosteroids, in order to increase the clinical and physiological efficacy, and to improve the ultimate outcome of pulmonary sarcoidosis.

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Appendix

In addition to the authors, the following investigators and institutions were members of the Dutch Study Group on Pulmonary Sarcoidosis, and participated in the study: Departments of Pulmonology: Twenteborg Hospital, Almelo (H.E.J. Sinninghe Damsté); University Hospital Vrije Universiteit, Amsterdam (J. Stam, P. Baas); Onze Lieve Vrouwe Gasthuis, Amsterdam (J.P.M. Wagenaar, W.B.G.J. Hamersma, W.B. Daalder, P. Hooghiemstra); Slotervaart Hospital, Amsterdam (P.I. van Spiegel, G. Visschers); Juliana-Lukas Hospital, Apeldoorn (A.J. van Harreveld); University Hospital Groningen, Groningen (H.J. Sluiter, G.H. Koëter, R. Aalbers); Westeinde Hospital, The Hague (J.J.P. de Hertog, C.R. Apap); Spaarne Hospital, Haarlem (P.W.J. Wiers, F.J.M. van Breukelen); Midden Twente Hospital, Hengelo (J.P.H.M. Creemers, A.P.M. Greefhorst); Groot Ziekengasthuis, Hertogenbosch (J.C.L.M.H. van Opstal, F. Beaumont); University Hospital St. Radboud, Nijmegen (J. Festen); University Hospital Dijkzigt, Rotterdam (C. Hilvering, H.C. Hoogsteden, S.E. Overbeek); St. Elisabeth Hospital, Tilburg (J.F.W.M. Molkenboer and M.C.P.J. Verpalen). Department of Pathology: St. Antonius Hospital, Nieuwegein (Sj.Sc. Wagenaar).

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